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Relapse of polymyalgia rheumatica following adjuvanted influenza vaccine: A case-based review

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Abstract

Polymyalgia rheumatica (PMR) is the most common inflammatory rheumatological condition affecting individuals aged >50 years. There have been rare reports of PMR and other vasculitides developing within 3 months of influenza vaccination. Influenza is a major public health issue associated with seasonal increased mortality and intensified health care service use. Annual vaccination is the most effective intervention to prevent influenza, especially in elderly individuals. We report a severe “flare” of PMR in a 70-year-old patient after receiving the adjuvanted trivalent influenza vaccine, as recommended by the Joint Committee on Vaccination and Immunisations for this age group in the UK National Health Service in 2018-2019. The adverse event (AE) could be interpreted as the newly described autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) as both PMR and ASIA display hyperactive immune responses. Caution is warranted in the use of vaccine adjuvants in patients with PMR with pre-existing imbalance of B and T cell homeostasis. Rare AEs are important to individuals, and personalized medicine means we should move away from “one size fits all” for vaccines, as well as for therapeutics.

Keywords: Polymyalgia rheumatica, B-lymphocytes, vaccines, autoimmune inflammatory syndrome induced by adjuvants/ASIA syndrome, adjuvants, squalene

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Introduction

Polymyalgia rheumatica (PMR) is a common inflammatory joint disease in older individuals, associated with increases in serum acute phase reactants. Imaging techniques have highlighted the presence of bursitis in the majority and vasculitis in some, in keeping with the overlap with giant cell arteritis (GCA) (1). Rapid symptomatic relief is obtained with prednisolone, but relapses are common when the steroid dose is reduced. The etiology and pathogenesis of PMR remain obscure. Both genetic predisposition and environmental triggers are thought to play a role, but most research has explored the immunological aspects of the disease. Recently, it has been shown that the distribution of B cells is highly disturbed in PMR and GCA, and that B cells likely contribute to the enhanced interleukin-6 response seen in both diseases (2).

Immunization has been reported as a rare trigger for vasculitides; a recent review of 1797 adverse events (AEs) reported across three international databases found that PMR represented 9.2% of reported AEs and was more frequently associated with influenza vaccines (3). In a review of 21 cases of GCA/PMR developing within 3 months of influenza vaccination, the role that adjuvant or influenza virus antigen plays in triggering disease is discussed (4). Recently, one case of PMR has been described following influenza B infection (5).

Seasonal influenza infection is an important cause of death in older individuals. Recent data from Europe for 2016/2017 confirm that excess mortality, especially in people aged >65 years, was primarily explained by the circulation of influenza virus A (H3N2) (6). Indeed, seasonal epidemics of influenza can cause up to 5 million infections and 250,000-650,000 deaths annually, from not only respiratory illness but also acute myocardial infarction (7) and other complications. Vaccination is the most effective intervention to prevent influenza and its associated morbidity and mortality and hence is recommended annually, especially in high-risk individuals. In the United Kingdom, uptake and effectiveness of influenza vaccination in seasons from 2010/2011 to 2016/2017 was high in people aged >65 years, with 80% of the >75 years receiving the vaccine (8).

Influenza viruses are enveloped negative-sense, single-stranded, segmented RNA viruses that belong to the family Orthomyxoviridae and are grouped into four strains (A, B, C, and D). Only influenza strains A and

B cause seasonal infections in humans. The viral envelope contains two major glycoproteins, hemagglutinin (HA) and neuraminidase (NA), and currently, the hemagglutination inhibition antibody (Ab) titre is regarded as the best available parameter for predicting protection from influenza infection. Unfortunately, Ab responses and the protection elicited by available vaccines tend to be lower in older than in younger adults (9). This has led to the development of vaccines containing adjuvants which trigger a strong immune response at lower antigen doses (10); this is helpful not only in the elderly but also in the public health situation of a threatened epidemic/pandemic. One vaccine adjuvant MF59® (Novartis International AG, Basel, Switzerland) is a squalene-based oil-in-water emulsion that has been used in several registered pandemic and seasonal influenza vaccines since 1997. It has greater efficacy than non-adjuvanted vaccines, especially in reducing hospitalizations due to influenza-related complications (11). Hence in the UK, the Joint Committee on Vaccinations and Immunisations advised in October 2017 that FLUAD, an influenza vaccine containing MF59®, and HA should be used for the >65 years rather than non-adjuvanted vaccines. We describe a patient with PMR in whom this adjuvanted influenza vaccine preparation triggered a severe flare-up of disease and discuss the role of the adjuvant MF59®.

Case Presentation

A 65-year-old female presented in 2013 with pain and stiffness in her neck, girdle joints, and knees, particularly her left knee, preceded by

“flu-like” symptoms (dry cough and headache) during a trip to New South Wales, Australia. She recalled multiple mosquito bites, so the possibility of Ross River fever, the most common mosquito-borne disease in Australia, was considered. It is caused by an arthritogenic alphavirus, Ross River virus (RRV), and leads to debilitating musculoskeletal inflammatory disease that usually resolves in 3-6 months (12). Treatment is supportive, but her symptoms worsened despite “over the counter” non-steroidal anti-inflammatory medication. Her pain peaked in the mornings so that it became difficult to function before midday. She attended a general practitioner (GP) when blood tests revealed an elevated erythrocyte sedimentation rate (ESR) of 120 mm/h (normal <21 mm/h) and C-reactive protein (CRP) of 141.7 mg/L (normal <3.0 mg/L), decreased albumin of 31 g/L (normal 35-50 g/L), and high normal globulin fraction of 39 g/L (normal 20-39 g/L). Negative results were obtained for rheumatoid factor, antinuclear Ab, RRV IgG and IgM Ab, Barmah Forest virus (another alphavirus causing musculoskeletal disease) IgG and IgM Ab, and urinary Bence Jones protein.

In view of these results showing activation of the inflammatory cascade (13) and a family history of PMR (her father), she was commenced on prednisolone 15 mg daily according to the guidelines of the Royal College of Physicians, London. After just 3 days of prednisolone, she was reviewed by a rheumatology specialist in Sydney when she was already symptomatically improved, and repeat blood tests reflected this with an ESR of 90 mm/h and a CRP of 71.4 mg/L. Serum protein electrophoresis showed an increased alpha-1 globulin of 4.0 g/L (normal 0.3-2.0 g/L), alpha-2 globulin of 12.0 g/L (normal 4.0-8.5 g/L), and beta globulin of 10.0 g/L (normal 5.0-9.5 g/L) with no paraprotein detected on serum electrophoresis. Additional tests showed negative cyclic citrullinated peptide and neutrophil cytoplasmic antibody antibodies. After 6 weeks of prednisolone 15 mg daily, she was clinically 95% better, and her CRP was 3.3 mg/L. On follow-up, prednisolone dose was gradually reduced from 15 mg to 6 mg over 9 months in 2013. In the early 2014, she developed focal distal interphalangeal joint arthritis associated with some diurnal PMR symptoms so the glucocorticoid (GC) dose was temporarily increased to 7.5 mg daily. Since 2015, her GC dose has always been <5 mg daily and was maintained at 3/2.5 mg on alternate days for most of 2017/2018. Although her disease was in remission with normal ESR and CRP levels, attempts to discontinue steroids were unsuccessful owing to mild symptoms in the mornings.

The patient's influenza vaccination history over five decades of adulthood has proven to be difficult to ascertain accurately. As a health care professional working in a high-risk area for the last 20 years of her career, she followed UK public health advice and received influenza vaccination annually via her National Health Service employer. In addition to >20 influenza vaccinations over her working life, she had also received the adjuvant keyhole limpet hemocyanin (KLH), a large T lymphocyte dependent immunostimulating protein, when she volunteered in a study on the primary, secondary, and tertiary immune responses of normal individuals to KLH (14). The influenza vaccines that the patient received after commencing GC for her PMR are the following:

- 2015 *Intanza*-trivalent, split virion, inactivated virus (Sanofi Pasteur MSD) (on prednisolone 5 mg daily).
- 2016 *Fluarix Tetra*-quadrivalent, split virion, inactivated virus (GSK) (on prednisolone 3.5 mg daily).
- 2017 *FluQuadri*-quadrivalent split virion, inactivated virus (Sanofi Pasteur) (on prednisolone 3.0 mg daily).
- 2018 *Fluad*-adjuvanted trivalent vaccine, each 0.5 mL intramuscular injection contains at least 15 µg of HA (Seqirus) (on prednisolone 3.0/2.5 mg alt die).

After the vaccination in October 2018, she developed the usual local side effects but soon began to feel fatigue, myalgia, and arthralgia, particularly in her left knee, the predominant site of her debilitating severe pain at presentation of her PMR >5 years previously. She increased her daily steroid dose to 4-5 mg on alternate days, and at consultant review 2 weeks later, her ESR and CRP levels were normal. She hence pursued “self-help” with physiotherapy and exercise. Over the next 6 weeks, she deteriorated, and her left knee in particular became increasingly painful and swollen so that routine activities (e.g., getting out of the bath or down the stairs, gardening, cleaning, or driving her manual car) became very difficult, especially in the mornings. Indeed, mornings were spent attempting to get started on the day; she felt 91 not 71 years old. Two months after receiving FLUAD, she was convinced that the vaccination had caused a flare of her PMR, and she increased her GC dosage to 10 mg daily. Within a week, she was 70% improved. She was reviewed by her GP and specialist who reported the reaction to the Vaccine Adverse Event Reporting System (www.vaers.hhs.gov) and, via the yellow card system, to the Medicines and Healthcare products Regulatory Agency, UK. Eight months after the dose of prednisolone

Main Points

- PMR is a heterogeneous condition which overlaps with GCA. We describe a female patient who presented with severe acute PMR (CRP 141.7 mg/L) who was in remission on low-dose prednisolone but experienced a significant relapse after adjuvanted influenza vaccination.
- The patient, a health care worker, had previously received multiple annual non-adjuvanted influenza vaccines, implicating the vaccine adjuvant in her disease flare. Her symptoms could be interpreted as ASIA syndrome.
- Caution is warranted in the use of vaccine adjuvants in patients with PMR who have pre-existing imbalance of B and T cell homeostasis.
- Rare AEs are important to individuals, and personalized medicine means we should move away from “one size fits all” in vaccines, as well as in therapeutics.

was increased, she had weaned the dose back down to 5 mg daily which is still higher than her previous maintenance dose.

Discussion

The AE following influenza vaccination in this case is compatible with the rare cases of PMR developing within 3 months of vaccination previously reported (4). However, in view of the extensive influenza vaccination history in this health care worker, it is likely that the adjuvant component of the vaccine was responsible for the severe symptomatic relapse of her PMR.

The adjuvant in FLUAD is MF59®; it contains 10 mg of squalene per dose. Squalene is a naturally occurring substance found in plants and animals. It is a cholesterol precursor and obtained for commercial purposes primarily from shark liver oil. Over 22 million doses of squalene-containing influenza vaccines have been administered, and the safety of an MF59®-adjuvanted vaccine is well established through a large safety database (15). An alarm was raised when antibodies to squalene were detected in the blood of most patients affected by the chronic multisystem illness termed "Gulf War syndrome," but no significant association was subsequently found (16). However, a single intradermal injection of squalene can induce a chronic T cell-mediated arthritis in certain strains of rodents (17). The dependence of this animal model on CD4⁺ T cells suggested a role for genes within the major histocompatibility complex. Arthritis transfer experiments confirmed the importance of T cells, particularly CD4⁺ cells in inducing joint inflammation (18).

In 2011, a new syndrome termed "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA) was defined (19). ASIA syndrome is associated with individual genetic predisposition and results from exposure to factors triggering hyperactive immune responses. A number of animal models of systemic and organ specific "autoimmune" diseases induced by adjuvants provide a proof of concept (20). In a descriptive analysis of 300 cases in the international ASIA syndrome registry, arthralgia, myalgia, and chronic fatigue were the most frequently reported symptoms. Eighty-nine percent of patients were also diagnosed with another defined rheumatic/autoimmune condition (21). Further analysis of 500 cases confirmed that polygenic autoinflammatory diseases were significantly associated with exposure to influenza vaccination (odds ratio 10.98, 95% confidence interval 3.81-31.67), $p < 0.0001$ (22). Although our patient interpreted her symptoms of arthritis/bursitis, myalgia, and fatigue as a "flare" of her PMR, it remains

possible that it could be interpreted as ASIA syndrome as both display hyperactive immune responses.

In a study of patients with primary Sjögren's syndrome vaccinated twice with the squalene-adjuvanted inactivated split-virion H1N1 vaccine Pandemrix (GlaxoSmithKline, Brentford, UK), it was found that patients not only developed higher H1N1 IgG titers of greater avidity than healthy controls on vaccination, but off-target B cells were also triggered resulting in increased autoantibody titers (23). The authors concluded that "caution is warranted when considering vaccination in non-treated autoimmune patients."

Autoantibodies have been reported in patients with PMR/GCA against a broad spectrum of human autoantigens (24). Recently, an association between PMR/GCA and IgG autoantibodies against the N-terminal 27 amino acids of human ferritin heavy chain has been found; these were present in 92% of patients before initiation of treatment and 69% of patients with disease flares compared with 1% of healthy blood donors (25).

Adjuvants, such as squalene, may trigger off-target B cells by increasing the frequency of T follicular helper cells (26). Patients with untreated PMR already have activated dendritic cells and monocytes/macrophages, disturbed B cell homeostasis (2), and a significant change in the Th17 cell to Treg cell ratio that is skewed toward an increased Th17 cell response (27). Although this disturbed B and T cell homeostasis in PMR is corrected by prednisolone, it may be that the low maintenance GC dose in this case was inadequate to prevent off-target effects of the adjuvant, which the patient believes triggered her relapse.

One influenza vaccine is not the same as another, in terms of not only efficacy but also safety profile. For example, there is now consensus that the AS03-adjuvanted influenza vaccine is associated with an increased risk of narcolepsy (28). Future vaccines with novel adjuvants may lead to different AEs, and post marketing surveillance needs to be improved (29). In addition, emerging evidence suggests that the repeated influenza vaccinations given to this patient may not be favorable for the induction and quality of cellular responses which play a considerable role in cross-protective immunity to different influenza strains (30). The description of ASIA syndrome should prompt research into mechanisms and lead to personalized medicine in the field of vaccination. There is individual variation in immune responses to

vaccines and adjuvants, and rare AEs are important to individuals. Patient choice needs to be respected; the approach should not be "one size fits all" for those aged >65 years.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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